research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

"Artificial cell" for diabetes

"Home use of an artificial beta cell in type 1 diabetes" conjures up a vision of some huge cellular blob taken home in a glass tank and connected up with the circulation, probably by Peter Cushing in a white coat and half moon spectacles. In fact, the artificial beta cell is just a fanciful name for a closed loop insulin pump driven by a glucose sensor. It's the device we've been waiting for for decades. The trial recruited 33 adults from the United Kingdom, Germany, and Austria, and 25 children and adolescents from the UK. The comparator was a sensor augmented pump. The closed loop system produced overall better control and less nocturnal hypoglycaemia over 12 weeks; but if not connected properly to a working battery, it caused three episodes of significant hypoglycaemia. So a promising start for a device that would be used for a whole lifetime, and a great opportunity to do an international collaborative follow-up study. Come on guys, you can do this.

N Engl J Med 2015, doi:10.1056/NEJMoa1509351

Busy with mabs and lasers

When you last heard of ranibizumab, it was probably in the context of comparative trials in macular degeneration, showing that it is no more effective than the much cheaper bevacizumab. Here's another ranibizumab trial—this time for diabetic proliferative retinopathy—which received only limited funding from the manufacturers, although most of its investigators had received other payments from Novartis/Genentech. They report this non-inferiority trial with admirable restraint. In most respects, ranibizumab produced better results than the standard treatment (panretinal photocoagulation). Lasering the whole retina is bound to cause some damage, whereas the signal from this trial is that ranibizumab injections do not. But the authors content themselves with saying that "Although longer term follow-up is needed, ranibizumab may be a reasonable treatment alternative, at least through two years, for patients with proliferative diabetic retinopathy."

JAMA 2015, doi:10.1001/jama.2015.15217

Progesterone flops for miscarriage

The temptation to use some kind of placebo for people suffering the repeated anguish of failed pregnancy is great, and the very name "progesterone" has a ring of promise about it. But it's a false promise, as this large British trial confirms. Daily doses of 400 mg micronised progesterone used vaginally from confirmation of pregnancy up to 12 weeks made no difference to the live birth rate in women who had had previous recurrent miscarriages, compared with placebo. The good news though is that the live birth rate in the groups was 63-67%.

N Engl J Med 2015, doi:10.1056/NEJMoa1504927

LEAN week in the journals

If it wasn't such a lean week in the journals, I'm not sure I'd be writing about the LEAN trial, a phase 2 study of the effect of liraglutide on "non-alcoholic steatohepatitis" (NASH). This nasty sounding condition is a triumph of disease mongering, taking the well known association between obesity and a fatty looking liver and turning it into a life threatening illness. "[NASH] is now the most common cause of chronic liver disease worldwide and incurs a significantly increased risk of both liver related and cardiovascular disease related morbidity and mortality." In fact, the association between liver fat deposition and cardiovascular disease is exactly the same as neck fat deposition and cardiovascular disease. The prevalence of both went up steadily over two decades (it may have plateaued now) while the incidence of cardiovascular disease went steadily down. The absolute risk of liver morbidity and mortality "incurred by" having the NASH label is tiny among the 30-50% of adults given this label in western countries. The absolute risk from a bleeding complication from repeated liver biopsies would probably be greater, were you to inflict them on everyone with a fatty looking liver on ultrasound. Anyway, enter liraglutide. NovoNordisk, the Wellcome Trust, and the National Institute for Health Research funded this tiny 48 week trial in 52 people with a histological diagnosis of NASH. Nine people given liraglutide and two given placebo showed histological resolution at the end of the trial. Larger studies are sure to follow, and perhaps one day every fat person in the world, myself included, will be offered regular injections of liraglutide.

Lancet 2015, doi:http://dx.doi.org/10.1016/S0140-6736(15)00803-X

Good germs fail tiny babies

The adult large bowel contains 500-1000 different species of bacteria, whereas the bowel of a premature infant contains just a few *Enterobacteriaceae*, with relatively few of the lactobacilli and bifidobacteria that are typical in of the term "breast fed infant." So there was clear logic in this trial of the probiotic *Bifidobacterium breve* BBG-001 to reduce necrotising enterocolitis, late-onset sepsis, and death in preterm infants. It was carried out in 24 hospitals across southeast England and included 1315 infants born between 23 and 30 weeks' gestational age. Unfortunately the trial showed that *Bifidobacterium breve* BBG-001 is not the right germ for the job, with similar outcomes for placebo.

Lancet 2015, doi:http://dx.doi.org/10.1016/S0140-6736(15)01027-2

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Hip pain and radiographic signs of osteoarthritis

ORIGINAL RESEARCH Diagnostic test study

Association of hip pain with radiographic evidence of hip osteoarthritis

Kim C, Nevitt M C, Niu J, et al

Cite this as: *BMJ* 2015;351:h5983

Study question Is there concordance between hip pain and radiographic hip osteoarthritis?

Methods In this diagnostic test study, pelvic radiographs were assessed for hip osteoarthritis in two cohorts: the Framingham Osteoarthritis Study (community of Framingham, Massachusetts) and the Osteoarthritis Initiative (a multicentre longitudinal cohort study of osteoarthritis in the United States). Using visual representation of the hip joint, participants reported whether they had hip pain on most days and the location of the pain: anterior, groin, lateral, buttocks, or low back. In the Framingham study, participants with hip pain were also examined for hip pain with internal rotation. The authors analysed the agreement between radiographic hip osteoarthritis and hip pain, and for those with hip pain suggestive of hip osteoarthritis they calculated the sensitivity, specificity, positive predictive value, and negative predictive value of radiographs as the diagnostic test.

Study answer and limitations In the Framingham study (n=946), only 15.6% of hips in patients with frequent hip pain showed radiographic evidence of hip osteoarthritis, and 20.7% of hips with radiographic hip osteoarthritis were frequently painful. The sensitivity of radiographic hip osteoarthritis for hip pain localised to the groin was 36.7%, specificity 90.5%, positive predictive value 6.0%, and negative predictive value 98.9%. Results did not differ much for hip pain at other locations or for painful internal rotation. In the Osteoarthritis Initiative Study (n=4366), only 9.1% of hips in patients with frequent pain showed radiographic hip osteoarthritis, and 23.8% of hips with radiographic hip osteoarthritis were frequently painful. The sensitivity of definite radiographic hip osteoarthritis for hip pain localised to the groin was 16.5%, specificity 94.0%, positive predictive value 7.1%, and negative predictive value 97.6%. Results also did not differ much for hip pain at other locations.

What this study adds Hip pain was not present in many hips with radiographic osteoarthritis, and many painful hips did not show radiographic hip osteoarthritis. Most older participants with a high suspicion for clinical hip osteoarthritis (groin or anterior pain and/or painful internal rotation) did not have radiographic hip osteoarthritis, suggesting that in many cases, hip osteoarthritis might be missed if diagnosticians relied solely on hip radiographs.

Funding, competing interests, data sharing See the full paper on thebmj.com for funding. The authors have no competing interests. Additional data are available from bevochan@bu.edu.

COMMENTARY Treat patients, not radiographs

Hip pain is common, particularly among adults older than 50 years, and intuitively linked to osteoarthritis. Since osteoarthritis is a leading cause of pain and disability, we need a better understanding of its epidemiology, and better methods for identifying patients at risk of the debilitating consequences caused by symptomatic disease.[1 2 5 6]

Chan and colleagues help to address these issues in a cross sectional study of the association between self reported hip pain and radiographic findings.[7] Despite limitations, the study teaches us an important lesson: many patients with radiographic hip osteoarthritis do not have frequent hip pain, and many patients with frequent self reported groin or anterior hip pain (traditionally considered suspicious of osteoarthritis) do not have radiographic hip osteoarthritis.

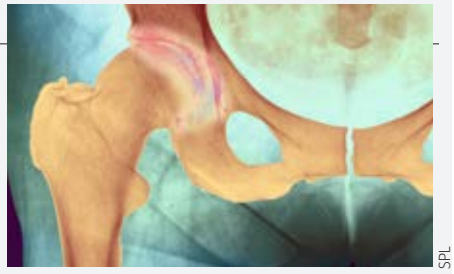
Generally, a firm diagnosis requires both symptoms of hip pain consistent with osteoarthritis and radiographic signs consistent with osteoarthritis. Patients with just one or the other are probably better described as having "clinical symptoms suggestive of degenerative hip joint disease" or "asymptomatic degenerative changes." Currently, a single reliable definition is lacking, which complicates both treatment and research.[3 4 9]

Given the substantial discordance between symptoms and radiographs, how should we respond to patients presenting with hip pain?

Radiographs are crucial to help rule out more serious conditions

In our opinion, hip radiographs should be obtained when a patient reports pain that cannot readily be explained by alternative diagnoses such as trochanteric bursitis, iliotibial band syndrome, or referred pain. Radiographs are crucial to help rule out more serious conditions such as osteonecrosis, (impending) stress fractures, transient osteoporosis, primary neoplasms, or metastatic bone disease.

Is it essential to add the diagnosis "hip joint osteoarthritis" to the diagnosis "hip pain" (or to "clinical symptoms suggestive of degenerative hip joint disease")? Patients with hip pain may benefit from lifestyle interventions, exercise programmes, or short term drug treatment, whether or not they have osteoarthritis, provided other causes have been ruled out. We currently have no effective method for slowing down the progression of hip osteoarthritis, so treatment regimens would be similar.[1 2 10 11] When patients seek help for hip pain that on clinical examination cannot readily be explained by alternative diagnoses, it is reasonable to obtain hip radiographs. When no abnormalities (other than osteoarthritis) are present, a trial of conservative management is reasonable if reviewed regularly with the option to progress to more intensive interventions if required. Similarly, when radiographic osteoarthritis is diagnosed in patients with few (or no) symptoms, lifestyle advice and a wait and see policy with optional follow-up is preferred. Ultimately, we must always remember to treat patients, not radiographs.



SPL

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Predicting pre-eclampsia

ORIGINAL RESEARCH Development and validation in two general population cohorts

Antenatal blood pressure for prediction of pre-eclampsia, preterm birth, and small for gestational age babies

Macdonald-Wallis C, Silverwood RJ, de Stavola BL, et al

Cite this as: *BMJ* 2015;351:h5948

Study question Can routine antenatal blood pressure measurements between 20 and 36 weeks' gestation contribute to the prediction of pre-eclampsia and its associated adverse outcomes?

Methods This study used repeated antenatal measurements of blood pressure from 12 996 women in the Avon Longitudinal Study of Parents and Children (ALSPAC) to develop prediction models and validated these in 3005 women from the Southampton Women's Survey (SWS). A model based on maternal early pregnancy characteristics only (BMI, height, age, parity, smoking, existing and previous gestational hypertension and diabetes, and ethnicity) plus initial mean arterial pressure was compared with a model additionally including current mean arterial pressure, a model including the deviation of current mean arterial pressure from a stratified normogram, and a model including both at different gestational ages from 20-36 weeks.

Study answer and limitations The addition of blood pressure measurements from 28 weeks onwards improved prediction models compared with use of early pregnancy risk factors alone, but they contributed little to the prediction of preterm birth or small for gestational age. Though multiple imputation of missing data was used to increase the sample size and minimise selection bias, the validation sample might have been slightly underpowered as the number of cases of pre-eclampsia was just below the recommended 100. Several risk factors were self reported, potentially introducing measurement error, but this reflects how information would be obtained in clinical practice.

What this study adds The addition of routinely collected blood pressure measurements from 28 weeks onwards improves predictive models for pre-eclampsia based on blood pressure in early pregnancy and other characteristics, facilitating a reduction in scheduled antenatal care.

Funding, competing interests, data sharing UK Wellcome Trust, US National Institutes of Health, and UK Medical Research Council. Other funding sources for authors are detailed in the full online paper. With the exceptions of CM-W, HMI, and KMG there were no competing interests.

COMMENTARY A challenge that shouldn't distract us from improving antenatal care across the board

A healthy mother and baby are the desired outcomes of all antenatal care, yet WHO estimates that every year around the world there are about 303 000 maternal deaths, 2.6 million stillbirths, and 2.7 million neonatal deaths. Pregnancy and birth are transformational life events, but optimal preparation for transition to motherhood often receives little attention.

Pregnancy is not an illness but comorbidities or complications can lead to mortality or serious morbidity. Risk stratification of pregnant women has been proposed to enable increased surveillance and appropriate prophylactic interventions for those at greater risk of complications, while normalising healthy women who have a high likelihood of uncomplicated pregnancy. Macdonald-Wallis and colleagues report the development and validation of a new prediction model for pre-eclampsia.[3]

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> The new model formalises some of the process that clinicians currently adopt informally at sequential antenatal visits

They conclude that incorporating routinely collected blood pressure measurements into models based on early pregnancy maternal characteristics would improve risk stratification, "facilitating a reduction in scheduled antenatal care" for those at low risk.

For many years, hypertensive disorders of pregnancy have been responsible for a substantial proportion of maternal deaths in high and low income countries. Thus it remains an important goal to predict and prevent pre-eclampsia to reduce morbidity and mortality in both mother and baby. But we must not ignore prediction and prevention of other adverse maternal and perinatal outcomes, and the promotion of health and wellbeing, if we are to achieve and exceed the millennium development goals to improve maternal health and reduce child mortality.

Around 70 risk prediction models have been reported for pre-eclampsia, but few undergo external validation and none has been tested against clinical judgment or widely introduced into widespread clinical practice. The new model formalises some of the processes that clinicians currently adopt informally at sequential antenatal visits—that is, adapting their perception of ongoing risk by incorporating new information on blood pressure. The model was good at ruling out disease. However, the positive predictive value of the basic and enhanced model was low.

The proposed benefit therefore comes from downscaling visits for the 30% of women who are judged to be low risk, but this would reduce the broader spectrum of antenatal interactions that occur at each visit, not just those related to pre-eclampsia. A Cochrane review on packages of antenatal care for low risk pregnant women found that women in all settings were less satisfied with a reduced schedule of visits, and for some women the gap between visits was perceived as too long.

Antenatal care is about much more than obtaining two numbers representing systolic and diastolic blood pressure. We should re-examine more holistically whether current schedules of care are fit for purpose and give women everywhere the best possible chance of a healthy pregnancy, a complication free delivery, and a healthy baby.

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Stepped care for depression and anxiety in visually impaired older adults

van der Aa H, van Rens G, Comijs H, et al

Cite this as: *BMJ* 2015;351:h6127

Study question Is stepped care compared with usual care effective in preventing the onset of major depressive, dysthymic, and anxiety disorders in older people with visual impairment (caused mainly by age related eye disease) and subthreshold depression and/or anxiety?

Methods 265 people aged ≥50 were randomly assigned to a stepped care programme plus usual care (n=131) or usual care only (n=134). Supervised occupational therapists, social workers, and psychologists from low vision rehabilitation organisations delivered the stepped care programme, which comprised watchful waiting, guided self help based on cognitive behavioural therapy, problem solving treatment, and referral to a general practitioner. The primary outcome was the 24 month cumulative incidence (seven measurements) of major depressive dysthymic and/or anxiety disorders (panic disorder, agoraphobia, social phobia, and generalised anxiety disorder). Secondary outcomes were change in symptoms of depression and anxiety, vision related quality of life, health related quality of life, and adaptation to vision loss over time up to 24 months' follow-up.

Study answer and limitations 62 participants (46%) in the usual care group and 38 participants (29%) from the stepped care group developed a disorder. The intervention was associated with a significantly reduced incidence (relative risk 0.63, 95% confidence interval 0.45 to 0.87; P=0.01), even if time to the event was taken into account (adjusted hazard ratio 0.57, 0.35 to 0.93; P=0.02). The number needed to treat was 5.8 (3.5 to 17.3). The dropout rate was fairly high (34.3%), but rates were not significantly different for the two groups, indicating that the intervention was as acceptable as usual care. Participants who volunteered and were selected for this study might not be representative of visually impaired older adults in general (responders were significantly younger than non-responders), thereby reducing the generalisability of the outcomes.

What this study adds Stepped care seems to be a promising way to deal with depression and anxiety in visually impaired older adults. This approach could lead to standardised strategies for the screening, monitoring, treatment, and referral of visually impaired older adults with depression and anxiety.

Funding, competing interests, data sharing Funded by ZonMw InZicht, the Dutch Organisation for Health Research and Development-InSight Society. There are no competing interests. Full dataset and statistical code are available from the corresponding author.
Study registration www.trialregister.nl NTR3296.

Cumulative incidence (No (%)) of depressive and/or anxiety disorders for stepped care (n=131) and usual care group (n=134)

	Baseline	3 months	6 months	9 months	12 months	18 months	24 months
Stepped care	0	20 (15.3)	27 (20.6)	28 (21.4)	32 (24.4)	37 (28.2)	38 (29.0)
Usual care	0	25 (18.7)	43 (32.1)	51 (38.1)	58 (43.3)	62 (46.3)	62 (46.3)

RESEARCH METHODS AND REPORTING

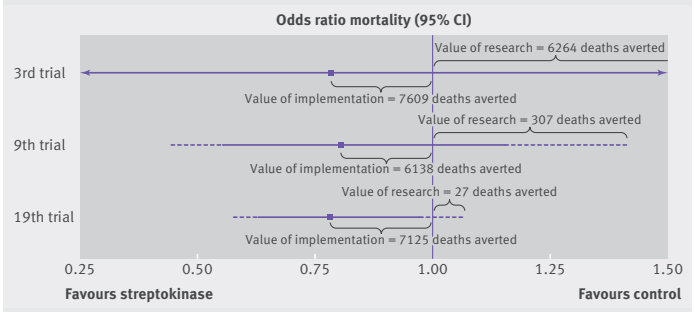
How to estimate the health benefits of additional research and changing clinical practice

Claxton K, Griffin S, Koffijberg H, McKenna C

Cite this as: *BMJ* 2015;351:h5987

Decisions about undertaking further research and at what point evidence should be implemented are important questions for research prioritisation and health policy. The results of standard meta-analysis can be extended to quantitatively assess the potential health benefits of gathering more evidence and of implementing the findings in a way that consideration of statistical significance cannot.

The uncertainty associated with whether an intervention is effective is indicated by the results of meta-analysis. By combining the estimated relative measure of effect (such as the odds ratio for mortality) with estimates of baseline risk and incidence, it is possible to estimate the health consequences of uncertainty. These consequences are the amount of health that could be lost from adopting a less effective intervention based on the balance of current evidence, and represent an upper limit on the potential health benefits of further research.



Expected benefits of implementation and potential benefits of further research

Health outcomes can also be improved by ensuring that existing research is better adopted in clinical practice. Combining the central estimate of relative effect from meta-analysis with estimates of baseline risk and incidence allows the expected health benefits of implementing research findings to be estimated.

To illustrate how the potential benefits of further research versus expected benefits of implementing current research findings can evolve, the figure shows three points in the sequence of 29 clinical trials that investigated early thrombolysis using streptokinase (versus no thrombolysis) after acute myocardial infarction.

In this example, the expected benefits of implementation quickly exceed the potential benefits of further research. However, early implementation might not be appropriate if its widespread use means that the type of research needed (for example, with adequate control) becomes impossible or more costly.